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(54) Title: METHODS FOR MODULATING AN IMMUNE RESPONSE BY MODULATING KRC ACTIVITY

(57) Abstract: This invention demonstrates that KRC molecules have multiple important functions as modulating agents in regulating a wide variety of cellular processes including: inhibiting NF $\kappa$ B transactivation, increasing TNF-alpha induced apoptosis, inhibiting JNK activation, inhibiting endogenous TNF-alpha expression, promoting immune cell proliferation and immune cell activation (e.g., in Th1 cells and/or Th2), activating IL-2 expression e.g., by activating the AP-1 transcription factor, and increasing actin polymerization. The present invention also demonstrates that KRC interacts with TRAF. Furthermore, the present invention demonstrates that KRC physically interacts with the c-Jun component of AP-1 to control its degradation. The present invention also demonstrates that KRC is downstream of several lymphocytic membrane receptors, including TNFR, TCR and TGF $\beta$ R. Upon TNFR signaling, KRC associates with the adaptor protein TRAF2 to inhibit NF $\kappa$ B and JNK-dependent gene expression. Upon TCR stimulation, KRC expression is rapidly induced and KRC physically associates with the c-Jun transcription factor to augment AP-1 dependent gene transcription. KRC knock-out (KO) T cells have impaired production of AP-1-dependent genes such as CD69 and IL-2. Upon TCR stimulation KRC also associates with the Th2-specific transcription factor GATA3, and T cells lacking KRC have impaired production of GATA3 dependent Th2 cytokines, IL-4, IL-5 and IL-13. Finally, upon TGF $\beta$  receptor signaling, KRC physically associates with the transcription factor SMAD3 to activate IgA germline transcription in B cells, since KRC KO B cells have impaired IgA production and germline IgA (GL $\alpha$ ) gene transcription. Methods for identifying modulators of KRC activity are provided. Methods for modulating an immune response and KRC-associated disorders using agents that modulate KRC expression and/or activity are also provided.

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